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PTO/SB/21 (08-03)

Approved for use through 07/31/2006. OMB 0651-0031

U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

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## TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	1623
Examiner Name	Lawrence E. Crane
Total Number of Pages in This Submission	31
Attorney Docket Number	NB 2008.01

### ENCLOSURES (check all that apply)

<input checked="" type="checkbox"/> Fee Transmittal Form  <input type="checkbox"/> Fee Attached  <input type="checkbox"/> Amendment / Reply  <input type="checkbox"/> After Final  <input type="checkbox"/> Affidavits/declaration(s)  <input type="checkbox"/> Extension of Time Request  <input type="checkbox"/> Express Abandonment Request  <input checked="" type="checkbox"/> Information Disclosure Statement  <input type="checkbox"/> Certified Copy of Priority Document(s)  <input type="checkbox"/> Response to Missing Parts/ Incomplete Application  <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s)  <input type="checkbox"/> Licensing-related Papers  <input type="checkbox"/> Petition  <input type="checkbox"/> Petition to Convert to a Provisional Application  <input type="checkbox"/> Power of Attorney, Revocation Change of Correspondence Address  <input type="checkbox"/> Terminal Disclaimer  <input type="checkbox"/> Request for Refund  <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance Communication to Group  <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences  <input type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)  <input type="checkbox"/> Proprietary Information  <input type="checkbox"/> Status Letter  <input checked="" type="checkbox"/> Other Enclosure(s) (please identify below):  <b>115 Reference, postcard receipt</b>		
<table><tr><td>Remarks</td><td></td></tr></table>			Remarks	
Remarks				

### SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Antoinette F. Konski Bingham McCutchen LLP
Signature	
Date	Aug. 6, 2004

### CERTIFICATE OF MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Mary R. Zimmerman		
Signature		Date	Aug 6, 2004

This collection of information is required by 37 CFR 1.51. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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**PTO FEE TRANSMITTAL**  
**for FY 2004**  
Effective 10/01/2003. Patent fees are subject to annual revision.  
☐ Application claims small entity status. See 37 CFR 1.27

**TOTAL AMOUNT OF PAYMENT** (\$) 180

**Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Examiner Name	Lawrence E. Crane
Art Unit	1623
Attorney Docket No.	NB 2008.01

**METHOD OF PAYMENT (check all that apply)**

☐ Check ☐ Credit card ☐ Money ☐ Other ☐ None  
Order

☒ Deposit Account:

Deposit Account Number: 50-2518

Deposit Account Name: Bingham McCutchen LLP

The Director is authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Credit any overpayments  
☐ Charge any additional fee(s) during the pendency of this application  
☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

**FEE CALCULATION**

**1. BASIC FILING FEE**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	
<b>SUBTOTAL (1)</b>					(\$ 0)

**2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE**

		Extra Claims	Fee from below	Fee Paid
Total Claims	-20 **	0	X	0
Independent Claims	-3 **	0	X	0
Multiple Dependent			X	0

Large Entity		Small Entity		Fee Description
Fee Code	Fee (\$)	Fee Code	Fee (\$)	
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent
<b>SUBTOTAL (2)</b> (\$ 0)				

\*\*or number previously paid, if greater; For Reissues, see above

**3. ADDITIONAL FEES**

Large Entity		Small Entity		Fee Description	Fee Paid
Fee Code	Fee (\$)	Fee Code	Fee (\$)		
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet.	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17 (q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	180
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR § 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR § 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	
Other fee (specify) _____					
*Reduced by Basic Filing Fee Paid					<b>SUBTOTAL (3)</b> (\$ 180)

**SUBMITTED BY**

Name (Print/Type)	Antoinette F. Koncki	Registration No. (Attorney/Agent)	34,202	Telephone	659-849-4950
Signature				Date	8-6-04

**WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**

This collection of information is required by 37 U.S.C. 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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AUG 09 2004

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Substitute for form 1449A-PTO

# **INFORMATION DISCLOSURE STATEMENT BY APPLICANT**

(use as many sheets as necessary)

Sheet 1 of 7

## **Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

## **U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number – Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	US-3,852,266	12-03-74	Kiyanagi et al.	
	2	US-4,247,544	01-27-81	Bergstrom, et al.	
	3	US-4,267,171	04-12-81	Bergstrom, et al.	
	4	US-4,542,210	09-17-85	Sakata et al.	
	5	US-4,668,777	05-26-87	Caruthers et al.	
	6	US-4,816,570	03-28-89	Farquhar	
	7	US-4,948,882	08-14-90	Ruth	
	8	US-4,963,263	10-16-90	Kauver	
	9	US-4,963,533	10-16-90	De Clercq et al.	
	10	US-4975,278	12-04-90	Senter et al.	

## **FOREIGN PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document Country Code <sup>3</sup> – Number <sup>4</sup> – Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
	11	DE 32 29 169 A1	02-09-84	De Clercq et al.		
	12	EP 0 311 107 A2	04-12-89	Stichting REGA VZW		
	13	EP 0 311 108A2	04-12-89	Stichting REGA VZW		
	14	EP 0 316 592	05-24-89	Stichting REGA VZW		
	15	GB 982 776	02-10-65	The Wellcome Foundation		
	16	RO 88451	01-30-86	Antibiotics Enterprise, Iasi		X
	17	WO 89/05817	06-29-89	Nucleic Acid Research Institute		
	18	WO 90/03978	04-19-90	Stichting REGA VZW		
	19	WO 91/17424	11-14-91	Vical, Inc.		

Examiner's  
SignatureDate  
Considered

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**Complete if Known**

Substitute for form 1449A-PTO

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT***(use as many sheets as necessary)*

Sheet 2 of 7

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number – Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	20	US-5,070,082	12-03-91	Murdock, et al. (I)	
	21	US-5,077,282	12-31-91	Murdock, et al. (II)	
	22	US-5,077,283	12-31-91	Murdock, et al. (III)	
	23	US-5,085,983	02-04-92	Scanlon	
	24	US-5,116,822	05-26-92	De Clercq et al.	
	25	US-5,116,827	05-26-92	Murdock, et al. (IV)	
	26	US-5,133,866	07-28-92	Kauver	
	27	US-5,137,724	08-11-92	Balzarini et al.	
	28	US-5,212,161	05-18-93	Moriniere et al.	
	29	US-5,212,291	05-18-93	Murdock, et al. (V)	

**FOREIGN PATENT DOCUMENTS**

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	30	WO 92/19767	11-12-92	Terrapin Technologies, Inc.		
	31	WO 93/06120	04-01-93	University of Rochester		
	32	WO 94/03467	02-17-94	Institute of Organic Chemistry & Biochemistry of the Academy of Sciences of the Czech Republic, et al.		
	33	WO 94/22483	10-13-94	Kozak, Alexander		

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	34	US-5,217,869	06-08-93	Kauver	
	35	US-5,233,031	08-03-92	Borch et al.	
	36	US-5,264,618	11-23-93	Felgner et al.	
	37	US-5,300,425	04-05-94	Kauver	
	38	US-5,338,659	08-16-94	Kauver, et al.	
	39	US-5,430,148	07-04-95	Webber, et al.	
	40	US-5,433,955	07-18-95	Bredehorst et al.	
	41	US-5,457,187	10-10-95	Gmeiner et al.	
	42	US-5,459,127	10-17-85	Felgner et al.	
	43	US-5,516,631	05-14-96	Frisch	

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	44	WO 95/01806	01-19-95	Kondratyev, A.		
	45	WO 95/08556	03-30-95	Amersham International, Inc.		
	46	WO 95/09865	04-13-95	Terrapin Technologies, Inc.		
	47	WO 95/12678	05-11-95	Connors, T. et al.		
	48	WO 96/03151	02-08-96	Springer et al.		
	49	WO 96/07413	04-04-96	University of Georgia Research Foundation & Yale University		

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	50	US-5,521,161	05-28-96	Malley et al.	
	51	US-5,527,900	06-18-96	Balzarini et al.	
	52	US-5,596,018	01-21-97	Baba et al.	
	53	US-5,616,564	04-01-97	Rapaport	
	54	US-5,627,165	05-06-97	Glazier	
	55	US-5,645,988	07-08-97	Vande Woude et al.	
	56	US-5,663,321	09-02-97	Gmeiner et al.	
	57	US-5,733,896	03-31-98	Holý et al.	
	58	US-5,798,340	08-25-98	Bischofberger et al.	
	59	US-5,968,910	10-19-99	Balzarini	

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	60	WO 96/10030	04-04-96	Isis Pharmaceuticals, Inc.		
	61	WO 96/23506	08-08-96	Fraunhofer Society for the Promotion of Applied Research E.V.		X
	62	WO 96/29336	09-26-96	Medical Research Council, University College Cardiff Consultants, Inc. Rega Foundation		

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	63	US-5,981,507	11-09-99	Josephson et al.	
	64	US-6,057,305	05-02-00	Holý et al.	
	65	US-6,245,750	06-12-01	Shepard	
	66	US-6,339,151	02-15-02	Shepard et al.	
	67	US-6,495,553	12-17-02	Shepard	
	68	US-2001/034440	10-25-01	Shepard et al.	
	69	US-2002/0147175	10-10-02	Shepard et al.	
	70	US-2002/0151519	10-17-02	Shepard et al.	

**FOREIGN PATENT DOCUMENTS**

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	71	WO 96/33168	10-24-96	Kumiai Chemical Industry Co Ltd et al.		
	72	WO 96/40088	12-19-96	Hostettler, Karl Y.		
	73	WO 96/40708	12-19-96	La Jolla Pharmaceuticals, Inc.		
	74	WO 96/40739	12-19-96	Terrapin Technologies, Inc.		
	75	WO 97/25342	07-17-97	Terrapin Technologies, Inc.		
	76	WO 97/28179	08-07-97	Fick, James & Israel, Mark		

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Sheet 6 of 7

**Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

**U.S. PATENT DOCUMENTS**

Examiner Initials*	Cite No. <sup>1</sup>	Document Number Number – Kind Code <sup>2</sup> (if known)	Publication Date MM-DD-YY	Name of Patentee or Application of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear

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	77	WO 97/49717	12-31-97	Balzarini et al.		
	78	WO 98/49177	11-05-98	University College Cardiff Consultants Limited		
	79	WO 99/06072	02-11-99	Boehringer Mannheim Corp.		
	80	WO 99/08110	02-18-99	NewBiotics, Inc.		
	81	WO 99/20741	04-29-99	Geron Corporation		
	82	WO 99/23104	05-14-99	The Government of the United States of America represented by The Secretary of Health & Human Services		
	83	WO 99/37753	07-29-99	NewBiotics, Inc.		

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Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
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Attorney Docket Number	NB 2008.01

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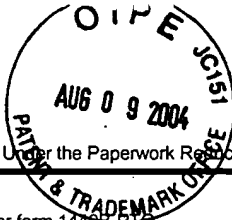
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	84	WO 00/18755	04-06-00	University College Cardiff Consultants Limited and Rega Foundation		
	85	WO 00/33888	06-15-00	Dubois, V. et al.		
	86	WO 01/07088	02-01-01	NewBiotics, Inc.		
	87	WO 01/83501	11-08-01	University College Cardiff Consultants Limited and Rega Foundation		
	88	WO 01/85749	11-15-01	University College Cardiff Consultants Limited and Rega Foundation		

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Sheet 1 of 19

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Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

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	1	ABRAHAM et al. "Synthesis and biological activity of aromatic amino acid phosphoramidates of 5-fluoro-2'-deoxyuridine and 1- $\beta$ -arabinofuranosylcytosine: Evidence of phosphoramidase activity" <i>J. Med. Chem.</i> (1996) <b>39</b> :4569-4575	
	2	AKDAS et al. "Glutathione S-transferase and multidrug-resistant phenotype in transitional cell carcinoma of the bladder" <i>Eur. Urol.</i> (1996) <b>29</b> (4):483-486	
	3	ALMASAN et al. "Deficiency of retinoblastoma protein leads to inappropriate S-phase entry, activation of E2F-responsive genes, and apoptosis" <i>PNAS, USA</i> (June 1995) <b>92</b> :5436-5440	
	4	ALMASAN et al. "Genetic instability as a consequence of inappropriate entry into and progression through S-phase" <i>Cancer Metast. Rev.</i> (1995) <b>14</b> :59-73	
	5	ANGLADA et al. "N,N'-cyclization of carbodiimides with 2-(bromomethyl)acrylic acid. A direct entry to the system 5-methylene-6H-pyrimidine-2,4-dione, A new class of thymine analogues" <i>J. Heterocyclic Chem.</i> (July-Aug. 1996) <b>33</b> :1259-1270	
	6	ANTELMAN et al. "Inhibition of tumor cell proliferation in vitro and in vivo by exogenous p110 <sup>RB</sup> , the retinoblastoma tumor suppressor protein" <i>Oncogene</i> (1995) <b>10</b> :697-704	
	7	ASAKURA and ROBINS, "Cerium(IV) catalyzed iodination at C5 of uracil nucleosides" <i>Tetrahedron Lett.</i> (1988) <b>29</b> (23):2855-2858	
	8	ASAKURA et al. "Cerium(IV)-mediated halogenation at C-5 of uracil derivatives" <i>J. Org. Chem.</i> (1990) <b>55</b> :4928-4933	
	9	ASCHELE et al. "Immunohistochemical quantitation of thymidylate synthase expression in colorectal cancer metastases predicts for clinical outcome to fluorouracil-based chemotherapy" <i>J. Clin. Oncol.</i> (June 1999) <b>17</b> (6):1760-1770	
	10	BAGSHAW, K.D. "Antibody-directed enzyme prodrug therapy: A review", <i>Drug Develop. Res.</i> (1995) <b>34</b> (2):220-230	
	11	BAJETTA et al. "A pilot safety study of capecitabine, a new oral fluoropyrimidine, in patients with advanced neoplastic disease" <i>Tumori</i> (1996) <b>82</b> :450-452	
	12	BALZARINI et al. "Incorporation of 5-substituted pyrimidine nucleoside analogues into DNA of a thymidylate synthetase-deficient murine FM3A carcinoma cell line" <i>Meth. Find. Exp. Clin. Pharmacol.</i> (1985) <b>7</b> (1):19-28	
	13	BALZARINI et al. "The cytostatic activity of 5-(1-azidovinyl)-2'-deoxyuridine (AzVDU) against herpes simplex virus thymidine kinase gene-transfected FM3A cells is due to inhibition of thymidylate synthase and enhanced by UV light ( $\lambda = 254$ nm) exposure" <i>FEBS Lett.</i> (1995) <b>373</b> :41-44	

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Sheet 2 of 19

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Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

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	14	BALZARINI et al. "Mechanism of anti-HIV action of masked alaninyl d4T-MP derivatives" <i>PNAS USA</i> (July 1996) <b>93</b> :7295-7299	
	15	BANERJEE et al. "Molecular mechanisms of resistance to antifolates, a review" <i>Acta Biochim. Pol.</i> (1995) <b>42</b> (4):457-464	
	16	BANERJEE et al. "Role of E2F-1 in chemosensitivity" <i>Cancer Res.</i> (Oct. 1, 1998) <b>58</b> :4292-4296	
	17	BARBATO et al. "Synthesis of bridged pyrimidine nucleosides and triazo [4, 3-c] pyrimidine nucleoside analogues" <i>Nucleos. Nucleot.</i> (1989) <b>8</b> (4):515-528	
	18	BARBOUR et al. "A naturally occurring tyrosine to histidine replacement at residue 33 of human thymidylate synthase confers resistance to 5-fluoro-2'-deoxyuridine in mammalian and bacterial cells" <i>Mol. Pharmacol.</i> (1992) <b>42</b> :242-248	
	19	BARR et al. "Reaction of 5-ethynyl-2'-deoxyuridylate with thiols and thymidylate synthetase" <i>Biochemistry</i> (1983) <b>22</b> :1696-1703	
	20	BARRETT "Trapping of the C5 methylene intermediate in thymidylate synthase" <i>J. Am. Chem. Soc.</i> (1998) <b>120</b> :449-450	
	21	BENZARIA et al. "Synthesis, <i>in vitro</i> antiviral evaluation, and stability studies of bis(S-acyl-2-thioethyl) ester derivatives of 9-[2-(phosphonomethoxy)ethyl]adenine (PMEA) as potential PMEA prodrugs with improved oral bioavailability" <i>J. Med. Chem.</i> (1996) <b>39</b> :4958-4965	
	22	BERGSTROM et al. "Synthesis of (E)-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridine and related analogues: Potent and unusually selective antiviral activity of (E)-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridine against herpes simplex virus type 1" <i>J. Med. Chem.</i> (1984) <b>27</b> :279-284	
	23	BERTINO et al. "Resistance mechanisms to methotrexate in tumors" <i>Stem Cells</i> (1996) <b>14</b> :5-9	
	24	BIGGE et al. "Palladium-catalyzed coupling reactions of uracil nucleosides and nucleotides" <i>J. Amer. Chem. Soc.</i> (Mar. 12, 1980) <b>102</b> (6):2033-2038	
	25	BUDAVARI (July 1996) (Ed.), <i>The Merck Index</i> , 12 <sup>th</sup> Edition, Doxifluridine, page 3493	
	26	BUDAVARI (July 1996) (Ed.), <i>The Merck Index</i> , 12 <sup>th</sup> Edition, Floxuridine, page 4148	
	27	BUDAVARI (July 1996) (Ed.), <i>The Merck Index</i> , 12 <sup>th</sup> Edition, Idoxuridine, page 4934	
	28	CALLAHAN et al. "Rhenium-188 for therapeutic applications from an alumina-based tungsten-188/rhenium-188 radionuclide generator" <i>Nuc-Compact</i> (Jan 1989) <b>20</b> :3-6	
	29	CARRERAS and SANTI "The catalytic mechanism and structure of thymidylate synthase" <i>Annu. Rev. Biochem.</i> (1995) <b>64</b> :721-762	
	30	CARTER et al. "Humanization of an anti-p185 <sup>HER2</sup> antibody for human cancer therapy" <i>PNAS USA</i> (May 1992) <b>89</b> :4285-4289	

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19

Application Number

10/681,418

Filing Date

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First Named Inventor

H. Michael SHEPARD

Art Unit

Lawrence E. Crane

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	31	CASS et al. "Recent advances in the molecular biology of nucleoside transporters of mammalian cells" <i>Biochem. Cell Biol.</i> (1998) <b>76(5)</b> :761-770	
	32	CATUCCI et al. "Development and significance of the HIV-1 reverse transcriptase M184V mutation during combination therapy with lamivudine, zidovudine, and protease inhibitors" <i>J. Acquir. Immune Defic. Syndr.</i> (July 1999) <b>21(3)</b> :203-208	
	33	CHAUDHURI and KOOL "Very high affinity DNA recognition by bicyclic and cross-linked oligonucleotides" <i>J. Am. Chem. Soc.</i> (1995) <b>117</b> :10434-10442	
	34	CHEN et al. "Sensitization of human breast cancer cells to cyclophosphamide and ifosfamide by transfer of a liver cytochrome P450 gene" <i>Cancer Res.</i> (Mar. 15, 1996) <b>56</b> :1331-1340	
	35	CHO and JOHNSON "(E)-5-(3-oxopropen-1-yl)-2'-deoxyuridine and (E)-5-(3-oxopropen-1-yl)-2',3'-dideoxyuridine; New antiviral agents: Synthesis and biological activity" <i>Tetrahedron Lett.</i> (1994) <b>35(8)</b> :1149-1152	
	36	CLARKE "Animal models of breast cancer: Their diversity and role in biomedical research" <i>Breast Cancer Res. Tr.</i> (1996) <b>39</b> :1-6	
	37	COBLEIGH et al. "Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease" <i>J. Clin. Oncol.</i> (Sept. 1999) <b>17(9)</b> :2639-2648	
	38	CODERRE et al. "Mechanism of action of 2',5-difluoro-1-arabinosyluracil" <i>J. Med. Chem.</i> (1983) <b>26(8)</b> :1149-1152	
	39	CONNORS and KNOX "Prodrugs in cancer chemotherapy" <i>Stem Cells</i> (1995) <b>13</b> :501-511	
	40	COPUR et al. "Thymidylate synthase gene amplification in human colon cancer cell lines resistant to 5-fluorouracil" <i>Biochem. Pharmacol.</i> (1995) <b>49(10)</b> :1419-1426	
	41	COSTI et al. "Phthalein derivatives as a new tool for selectivity in thymidylate synthase inhibition" <i>J. Med. Chem.</i> (1999) <b>42(12)</b> :2112-2124	
	42	CRISP "Synthesis of 5-alkenyl-2'-deoxyuridines via organostannanes" <i>Synth. Commun.</i> (1989) <b>19(11 &amp; 12)</b> :2117-2123	
	43	CRUICKSHANK et al. "Oligonucleotide labelling: A concise synthesis of a modified thymidine phosphoramidite" <i>Tetrahedron Lett.</i> (1988) <b>29(41)</b> :5221-5224	
	44	DALE et al. "The synthesis and enzymatic polymerization of nucleotides containing mercury: Potential tools for nucleic acid sequencing and structural analysis" <i>PNAS USA</i> (August 1973) <b>70(8)</b> :2238-2242	

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	45	DeCLERCQ et al. "Antiviral Activity of Novel Deoxyuridine Derivatives" <u>Current Chemotherapy: Proceedings of the International Congress of Chemotherapy</u> published in <i>Virology</i> (Sept. 18, 1978) 1:352-354	
	46	DeCLERCQ et al. "Nucleic acid related compounds. 40. Synthesis and biological activities of 5-alkynyluracil nucleosides" <i>J. Med. Chem.</i> (1983) 26:661-666	
	47	DeCLERCQ "Antiviral Activity Spectrum and Target of Action of Different Classes of Nucleoside Analogues" <i>Nucleos. Nucleot.</i> (1994) 13(6&7):1271-1295	
	48	DICKER et al. "Methotrexate resistance in an <i>in vivo</i> mouse tumor due to a non-active-site dihydrofolate reductase mutation" <i>PNAS USA</i> (Dec. 1993) 90:11797-11801	
	49	DIRVIN et al. "The role of human glutathione S-transferase isoenzymes in the formation of glutathione conjugates of the alkylating cytostatic drug thiotepa" <i>Cancer Res.</i> (April 15, 1995) 55:1701-1706	
	50	DORR and von HOFF "PALA" <i>In: Cancer Chemotherapy Handbook</i> , 2nd Edition, Appleton & Lange, Norwalk, Connecticut (1994) pp. 768-773	
	51	DUNN et al. "Solution of the conformation and alignment tensors for the binding of trimethoprim and its analogs to dihydrofolate reductase: 3D-quantitative structure-activity relationship study using molecular shape analysis, 3-way partial least-squares regression, and 3-way factor analysis" <i>J. Med. Chem.</i> (1996) 39:4825-4832	
	52	DYER et al. "Nucleic Acids Chemistry: Improved and new synthetic procedures, methods, and techniques" Townsend, L. B. & Tipson, R. S., eds. (Wiley-Interscience, New York, NY) (1991) 4:79-83	
	53	EDLER et al. "Immunohistochemically detected thymidylate synthase in colorectal cancer: An independent prognostic factor of survival" <i>Clinical Cancer Research</i> (Feb. 2000) 6:488-492	
	54	FAN and BERTINO "Functional roles of E2F in cell cycle regulation" <i>Oncogene</i> (1997) 14:1191-1200	
	55	FARQUHAR et al. "Synthesis and antitumor evaluation of bis[(pivaloyloxy)methyl] 2'-deoxy-5-fluorouridine 5'-monophosphate (FdUMP): A strategy to introduce nucleotides into cells" <i>J. Med. Chem.</i> (1994) 37:3902-3909	
	56	FARQUHAR et al. "5'-[4-pivaloyloxy]-1,3,2-dioxaphosphorinan-2-yl]-2'-deoxy-5-fluorouridine: A membrane-permeating prodrug of 5-fluoro-2'-deoxyuridylic acid (FdUMP)" <i>J. Med. Chem.</i> (1995) 38:488-495	
	57	FARROW et al. "Synthesis and biological properties of novel phosphotriesters: A new approach to the introduction of biologically active nucleotides into cells" <i>J. Med. Chem.</i> (1990) 33(5):1400-1406	

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STATEMENT BY APPLICANT**

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Sheet 5 of 19

**Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

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	58	FELMINGHAM and WASHINGTON "Trends in the antimicrobial susceptibility of bacterial respiratory tract pathogens – findings of the Alexander Project 1992-1996" <i>J. Chemotherapy</i> (1999) 11(Suppl 1):5-21	
	59	FREED et al. "Evidence for acyloxymethyl esters of pyrimidine 5'-deoxyribonucleotides as extracellular sources of active 5'-deoxyribonucleotides in cultured cells" <i>Biochem. Pharmacol.</i> (1989) 38(19):3193-3198	
	60	FREEMANTLE et al. "Molecular characterisation of two cell lines selected for resistance to the folate-based thymidylate synthase inhibitor, ZD1694" <i>Brit. J. Cancer</i> (1995) 71:925-930	
	61	FRIES et al. "Synthesis and biological evaluation of 5-fluoro-2'-deoxyuridine phosphoramidate analogs" <i>J. Med. Chem.</i> (1995) 38(14):2672-2680	
	62	FUNK "Cancer cell cycle control" <i>Anticancer Research</i> (1999) 19:4772-4780	
	63	GOLDSTEIN and BROWN "Genetic aspects of disease" In: <i>Harrison's Principles of Internal Medicine</i> , 12th Edition, McGraw-Hill, Inc., New York, NY (1991) pp. 21-76	
	64	GOODWIN et al. "Incorporation of alkylthiol chains at C-5 of deoxyuridine" <i>Tetrahedron Lett.</i> (1993) 34(35):5549-5552	
	65	GOTTESMANN et al. "Genetic analysis of the multidrug transporter" <i>Annu. Rev. Genet.</i> (1995) 29:607-649	
	66	GRAHAM et al. "DNA duplexes stabilized by modified monomer residues: Synthesis and stability" <i>J. Chem. Soc. Perkin Trans.</i> (1998) 1:1131-1138	
	67	GRIENGL et al. "Phosphonoformate and phosphonoacetate derivatives of 5-substituted 2'-deoxyuridines: Synthesis and antiviral activity" <i>J. Med. Chem.</i> (1988) 31(9):1831-1839	
	68	HOBBS, Jr. "Palladium-catalyzed synthesis of alkynylamino nucleosides. A universal linker for nucleic acids" <i>J. Org. Chem.</i> (1989) 54:3420-3422	
	69	HOOKER et al. "An in vivo mutation from leucine to tryptophan at position 210 in human immunodeficiency virus type 1 reverse transcriptase contributes to high-level resistance to 3'-azido-3'-deoxythymidine" <i>J. Virol.</i> (Nov. 1996) 70(11):8010-8018	
	70	HOSTETLER et al. "Enhanced oral absorption and antiviral activity of 1-O-octadecyl-sn-glycero-3-phospho-acyclovir and related compounds in hepatitis B virus infection, in vitro" <i>Biochem. Pharmacol.</i> (1997) 53:1815-1822	
	71	HOUZE, et al. "Detection of thymidylate synthase gene expression levels in formalin-fixed paraffin embedded tissue by semiquantitative, nonradioactive reverse transcriptase polymerase chain reaction" <i>Tumor Biol.</i> (1997) 18:53-68	

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Application Number

10/681,418

Filing Date

October 7, 2003

First Named Inventor

H. Michael SHEPARD

Art Unit

Lawrence E. Crane

Examiner Name

1623

Attorney Docket Number

NB 2008.01

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	72	HSAIO and BARDOS "Synthesis of 5'-thymidinyl bis(1-aziridinyl)phosphinates as antineoplastic agents" <i>J. Med. Chem.</i> (19810 24:887-889	
	73	HUDZIAK et al. "Amplified expression of the HER2/ERBB2 oncogene induces resistance to tumor necrosis factor $\alpha$ in NIH 3T3 cells" <i>PNAS USA</i> (July 1988) 85:5102-5106	
	74	HUSAIN et al. "Elevation of topoisomerase I messenger RNA, protein, and catalytic activity in human tumors: Demonstration of tumor-type specificity and implications for cancer chemotherapy" <i>Cancer Research</i> (Jan. 15, 1994) 54:539-546	
	75	JACKMAN and CALVERT "Folate-based thymidylate synthase inhibitors as anticancer drugs" <i>Ann. Oncol.</i> (1995) 6(9):871-881	
	76	JACKMAN et al. "Quinazoline-based thymidylate synthase inhibitors: Relationship between structural modifications and polyglutamation" <i>Anti-Cancer Drug Design</i> (1995) 10:573-589	
	77	JOHNSTON et al. "Thymidylate synthase gene and protein expression correlate and are associated with response to 5-fluorouracil in human colorectal and gastric tumors" <i>Cancer Res.</i> (April 1, 1995) 55:1407-1412	
	78	JONES and MANN "New methods of synthesis of $\beta$ -aminoethylpyrazoles" <i>J. Am. Cancer Soc.</i> (Aug. 20, 1953) 75:4048-4052	
	79	KASHANI-SABET et al. "Detection of drug resistance in human tumors by <i>in vitro</i> enzymatic amplification" <i>Cancer Res.</i> (Oct. 15, 1988) 48:5775-5778	
	80	KOBAYASHI et al. "Effect of hammerhead ribozyme against human thymidylate synthase on the cytotoxicity of thymidylate synthase inhibitors" <i>Jpn. J. Cancer Res.</i> (Nov. 1995) 86:1014-1018	
	81	KOMAKI et al. "Difference in thymidylate synthetase activity in involved nodes compared with primary tumor in breast cancer patients" <i>Breast Cancer Res. Tr.</i> (1995) 35(2):157-162	
	82	KRAJEWSKA and SHUGAR "Pyrimidine ribonucleoside phosphorylase activity VS 5- and/or 6-substituted uracil and uridine analogues, including conformational aspects" <i>Biochem. Pharmacol.</i> (1982) 31(6):1097-1102	
	83	KWONG et al. "Hepatitis C virus NS3/4A protease" <i>Antivir. Res.</i> (1999) 41:67-84	
	84	LASIC "Doxorubicin in sterically stabilized liposomes" <i>Nature</i> (Apr. 11, 1996) 380:561-562	

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**Complete if Known****Application Number****10/681,418****Filing Date****October 7, 2003****First Named Inventor****H. Michael SHEPARD****Art Unit****Lawrence E. Crane****Examiner Name****1623****Attorney Docket Number****NB 2008.01****NON PATENT LITERATURE DOCUMENTS**

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	85	LEE et al. "Inhibition of mouse thymidylate synthase promoter activity by the wild-type p53 tumor suppressor protein" <i>Exp. Cell Res.</i> (1997) <b>234</b> :270-276	
	86	LENZ et al. "p53 and thymidylate synthase expression in untreated stage II colon cancer: associations with recurrence, survival, and site" <i>Clinical Cancer Research</i> (May 1998) <b>4</b> :1227-1234	
	87	LEŠ et al. "Modeling of reaction steps relevant to deoxyuridylate (dUMP) enzymatic methylation and thymidylate synthase mechanism-based inhibition" <i>Journal of Biomolecular Structure &amp; Dynamics</i> (1998) <b>15</b> (4):703-715	
	88	LEWIS et al. "Differential responses of human tumor cell lines to anti-p185 <sup>HER2</sup> monoclonal antibodies" <i>Cancer Immunol. Immunother.</i> (1993) <b>37</b> (4):255-263	
	89	LEWIS et al. "A serum-resistant cytofection for cellular delivery of antisense oligodeoxynucleotides and plasmid DNA" <i>PNAS USA</i> . (April 1996) <b>93</b> :3176-3181	
	90	LIN et al., "Rhenium188 hydroxyethylidene diphosphonate: a new generator-produced radiotherapeutic drug of potential value for the treatment of bone metastases" <i>Eur. J. Nucl. Med.</i> <b>24</b> (6):590-595 (June 1997)	
	91	LIVAK et al. "Detection of single base differences using biotinylated nucleotides with very long linker arms" <i>Nucl. Acids Res.</i> (1992) <b>20</b> (18):4831-4837	
	92	LIVINGSTON et al. "Studies with tetrahydrohomofolate and thymidylate synthetase from amethopterin-resistant mouse leukemia cells" <i>Biochemistry</i> (Aug. 1968) <b>7</b> (8):2814-2818	
	93	LÖNN et al. "Higher frequency of gene amplification in breast cancer patients who received adjuvant chemotherapy" <i>Cancer</i> (Jan. 1, 1996) <b>77</b> (1):107-112	
	94	LOOK et al. "Increased thymidine kinase and thymidylate synthase activities in human epithelial ovarian carcinoma" <i>Anticancer Res.</i> (1997) <b>17</b> :2353-2356	
	95	LOVEJOY et al. "Animal models and the molecular pathology of cancer" <i>J. Pathol.</i> (1997) <b>181</b> :130-135	
	96	MADEC et al. "Some characteristics of fetal and adult isoenzymes of thymidine kinase in human breast cancers" <i>Bull. Cancer</i> (1998) <b>75</b> :187-194	
	97	MADER et al. "Resistance to 5-fluorouracil" <i>Gen. Pharma.</i> (1998) <b>31</b> (5):661-666	
	98	MAHALINGAM et al. "Structural and kinetic analysis of drug resistant mutants of HIV-1 protease" <i>Eur. J. Biochem.</i> (1999) <b>263</b> :238-245	
	99	McGUIGAN et al. "Certain phosphoramidate derivatives of dideoxy uridine (ddU) are active against HIV and successfully by-pass thymidine kinase" <i>FEBS Let</i> (1994) <b>351</b> :11-14	

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Filing Date	October 7, 2003
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Art Unit	Lawrence E. Crane
Examiner Name	1623
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	100	McINTEE "Probing the mechanism of action and decomposition of amino acid phosphomonoester amidates of antiviral nucleoside prodrugs" <i>J. Med. Chem.</i> (1997) <b>40</b> :3323-3331	
	101	MEAD et al. "Pharmacologic aspects of homofolate derivatives in relation to amethopterin-resistant murine leukemia" <i>Cancer Res.</i> (Nov. 1966) <b>26(1)</b> :2374-2379	
	102	MEIER et al. "ADA-bypass by lipophilic cyclosal-ddAMP pro-nucleotides a second example of the efficiency of the cyclosal-concept" <i>Bioorg. Med. Chem. Lett.</i> (1997) <b>7(12)</b> :1577-1582	
	103	MEIER et al. "Cyclic saligenyl phosphotriesters of 2',3'-dideoxy-2',3'-didehydrothymidine (d4T) - a new pro-nucleotide approach" <i>Bioorg. Med. Chem. Lett.</i> (1997) <b>7(2)</b> :99-104	
	104	MEIER et al. "CycloSal-pro-nucleotides: The design and biological evaluation of a new class of lipophilic nucleotide prodrugs" <i>Int'l. Antiviral News</i> (1997) <b>5(10)</b> :183-185	
	105	MELTON et al. "Antibody-directed enzyme prodrug therapy (ADEPT). Review article" <i>Drugs of the Future</i> (1996) <b>21(2)</b> :167-181	
	106	MELTON and SHERWOOD "Antibody-enzyme conjugates for cancer therapy" <i>J. Natl. Cancer Inst.</i> (Feb. 21, 1996) <b>88(3/4)</b> :153-165	
	107	MOBASHERY and JOHNSTON "Reactions of <i>Escherichia coli</i> TEM $\beta$ -lactamase with cephalothin and with C <sub>10</sub> -dipeptidyl cephalosporin esters" <i>J. Biol. Chem.</i> (June 15, 1986) <b>261(17)</b> :7879-7887	
	108	MOBASHERY et al. "Conscripting $\beta$ -lactamase for use in drug delivery. Synthesis and biological activity of a cephalosporin C <sub>10</sub> -ester of an antibiotic dipeptide" <i>J. Am. Chem. Soc.</i> (1986) <b>108</b> :1685-1686	
	109	MORGAN et al. "Tumor efficacy and bone marrow-sparing properties of TER286, a cytotoxin activated by glutathione S-transferase" <i>Cancer Res.</i> (June 15, 1998) <b>58</b> :2568-2575	
	110	MULDER et al. "Thymidylate synthase levels in tumor biopsies from patients with colorectal cancer" <i>Anticancer Res.</i> (1994) <b>14(6B)</b> :2677-2680	
	111	MURRAY "Antibiotic resistance" <i>Adv. Internal. Med.</i> (1997) <b>42</b> :339-367	
	112	NAGATA et al. "The role of HBV DNA quantitative PCR in monitoring the response to interferon treatment in chronic hepatitis B virus infection" <i>J. Hepatol.</i> (1999) <b>30</b> :965-969	
	113	NEGISHI et al. "Enhancement of N <sup>4</sup> -aminocytidine-induced mutagenesis by Ni <sup>++</sup> ion" <i>Nucl. Acids Symposium</i> (1996) <b>35</b> :137-138	
	114	NICHOL and HAKALA "Comparative growth-inhibitory activity of homofolic acid against cell lines sensitive and resistant to amethopterin" <i>Biochem. Pharmacol.</i> (Oct. 1966) <b>15(10)</b> :1621-1623	
	115	NICULESCU-DUVAZ and SPRINGER "Gene-directed enzyme prodrug therapy: A review of enzyme/prodrug combinations" <i>Expert Opin. Invest. Drugs</i> (1997) <b>6(6)</b> :685-703	

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Art Unit

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	116	PALMER et al. "Highly drug-resistant HIV-1 clinical isolates are cross-resistant to many antiretroviral compounds in current clinical development" <i>AIDS</i> (1999) <b>13(6)</b> :661-667	
	117	PARADISO et al. "Thymidilate synthase and p53 primary tumour expression as predictive factors for advanced colorectal cancer patients" <i>Brit. J. Cancer</i> (2000) <b>82(3)</b> :560-567	
	118	PATTERSON et al. "Thymidine phosphorylase moderates thymidine-dependent rescue after exposure to the thymidylate synthase inhibitor ZD1694 (tomudex) <i>in vitro</i> " <i>Cancer Res.</i> (July 1, 1998) <b>58</b> :2737-2740	
	119	PEDERSEN-LANE et al. "High-level expression of human thymidylate synthase" <i>Protein Expression and Purification</i> (1997) <b>10</b> :256-262	
	120	PEGRAM et al. "The effect of HER-2/ <i>neu</i> overexpression on chemotherapeutic drug sensitivity in human breast and ovarian cancer cells" <i>Oncogene</i> (1997) <b>15</b> :537-547	
	121	PESTALOZZI et al. "Prognostic importance of thymidylate synthase expression in early breast cancer" <i>J. Clin. Oncol.</i> (May 1997) <b>15(5)</b> :1923-1931	
	122	PHELPS et al. "Synthesis and biological activity of 5-fluoro-2'-deoxyuridine 5'-phosphorodiamidates" <i>J. Med. Chem.</i> (1980) <b>23</b> :1229-1232	
	123	PLUTA et al., "Synthesis and biological properties of 4-hydroxy, 4-thio-5-pyrimidine derivatives" <i>Boll. Chim. Farmaceutico</i> (Gennaio 1999) <b>138(1)</b> :30-33	
	124	ROBINS and BARR "Nucleic acid related compounds. 31. Smooth and efficient palladium-copper catalyzed coupling of terminal alkynes with 5-iodouracil nucleosides" <i>Tetrahedron Lett.</i> (1981) <b>22</b> :421-424	
	125	ROBINS et al. "Nucleic acid related compounds. 38. Smooth and high-yield iodination and chlorination at C-5 of uracil bases and <i>p</i> -toluyl-protected nucleosides" <i>Can. J. Chem.</i> (1982) <b>60</b> :554-557	
	126	ROBINS and BARR "Nucleic acid compounds. 39. Efficient conversion of 5-iodo to 5-alkynyl and derived 5-substituted uracil bases and nucleosides" <i>J. Org. Chem.</i> (1983) <b>48</b> :1854-1862	
	127	RODE "Specificity of thymidylate synthase inactivation by 4,5-bisubstituted dUMP analogues" <i>M. Nencki Inst. Exp. Biol., Acta Biochimica Polonica</i> (1993) <b>40(3)</b> :363-368	
	128	ROMAIN et al. "Prognostic value of cytosolic thymidine kinase activity as a marker of proliferation in breast cancer" <i>Int. J. Cancer</i> (1995) <b>61</b> :7-12	
	129	ROTH et al. "p53 tumor suppressor gene therapy for cancer" <i>Oncology</i> (1999) <b>13(10)(5)</b> :148-154	

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**Complete if Known**

Application Number

10/681,418

Filing Date

October 7, 2003

First Named Inventor

H. Michael SHEPARD

Art Unit

Lawrence E. Crane

Examiner Name

1623

Attorney Docket Number

NB 2008.01

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	130	RUTH and BERGSTROM "C-5 substituted pyrimidine nucleosides. 1. Synthesis of C-5 allyl, propyl, and propenyl uracil and cytosine nucleosides via organopalladium intermediates" <i>J. Org. Chem.</i> (1978) <b>43(14)</b> :2870-2876	
	131	SABOULARD et al. "Characterization of the activation pathway of phosphoramidate triester prodrugs of stavudine and zidovudine" <i>Mol. Pharmacol.</i> (1999) <b>56</b> :693-704	
	132	SANTI "Perspectives on the design and biochemical pharmacology of inhibitors of thymidylate synthetase" <i>J. Med. Chem.</i> (Feb. 1980) <b>23(2)</b> :103-111	
	133	SASTRY et al. "Membrane-permeable dideoxyuridine 5'-monophosphate analogue inhibits human immunodeficiency virus infection" <i>Mol. Pharmacol.</i> (1992) <b>41</b> :441-445	
	134	SATYAM et al. "Design, synthesis, and evaluation of latent alkylating agents activated by glutathione S-transferase" <i>J. Med. Chem.</i> (1996) <b>39</b> :1736-1747	
	135	SHAFFER and VUITTON "Highly active antiretroviral therapy (HAART) for the treatment of infection with human immunodeficiency virus type 1" <i>Biomed. &amp; Pharmacother.</i> (1999) <b>53</b> :73-86	
	136	SHEPARD and LEWIS "Resistance of tumor cells to tumor necrosis factor" <i>J. Clin. Immunol.</i> (1988) <b>8(5)</b> :333-341	
	137	SIMON and SCHINDLER "Cell biological mechanisms of multidrug resistance in tumors" <i>PNAS USA</i> (April 1994) <b>91</b> :3497-3504	
	138	SMITH et al. "Response to doxorubicin of cultured normal and cancerous human mammary epithelial cells" <i>JNCI</i> (Feb. 1985) <b>74(2)</b> :341-347	
	139	SMITH et al. "Preliminary correlations of clinical outcome with <i>in vitro</i> chemosensitivity of second passage human breast cancer cells" <i>Cancer Res.</i> (May 15, 1990) <b>50(10)</b> :2943-2948	
	140	SMITH et al. "Regulation and mechanisms of gene amplification" <i>Phil. Trans. R. Soc. Lond. B</i> (1995) <b>347</b> :49-56	
	141	STÜHLINGER et al. "Clinical therapy and HER-2 oncogene amplification in breast cancer: Chemo vs radiotherapy" <i>J. Steroid Biochem. Molec. Biol.</i> (1994) <b>49(1)</b> :39-42	
	142	SUGARMAN et al. "Recombinant human tumor necrosis factor- $\alpha$ : Effects on proliferation of normal and transformed cells <i>in vitro</i> " <i>Science</i> (Nov. 22, 1985) <b>230(4728)</b> :943-945	
	143	SUKI et al. "Risk classification for large cell lymphoma using lactate dehydrogenase, beta-2 microglobulin, and thymidine kinase" <i>Leukemia and Lymphoma</i> (1995) <b>18</b> :87-92	
	144	TANNOCK "Treatment of cancer with radiation and drugs" <i>J. Clin. Oncol.</i> (Dec. 1996) <b>14(12)</b> :3156-3174	

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	145	TEH et al. "Tumor suppressor genes (TSG)" <i>Anticancer Research</i> (1999) <b>19</b> :4715-4728	
	146	TOLSTIKOV et al. "Synthesis and DNA duplex stabilities of oligonucleotides containing C-5-(3-methoxypropynyl)-2'-deoxyuridine residues" <i>Nucleos. Nucleot.</i> (1997) <b>16</b> (3):215-225	
	147	TOUROTOGLOU and PAZDAR "Thymidylate synthase inhibitors" <i>Clin. Cancer Res.</i> (Feb. 1996) <b>2</b> (2):227-243	
	148	TROUTNER "Chemical and physical properties of radionuclides" <i>Nucl. Med. Biol.</i> (1987) <b>14</b> (3):171-176	
	149	TURNER and SUMMERS "Structural biology of HIV" <i>J. Mol. Biol.</i> (1999) <b>285</b> :1-32	
	150	VALETTE et al. "Decomposition pathways and <i>in vitro</i> HIV inhibitory effects of isodda pronucleotides: Toward a rational approach for intracellular delivery of nucleoside 5'-monophosphates" <i>J. Med. Chem.</i> (1996) <b>39</b> :1981-1990	
	151	van LAAR "Therapeutic efficacy of fluoropyrimidines depends on the duration of thymidylate synthase inhibition in the murine colon 26-B carcinoma tumor model" <i>Clin. Cancer Res.</i> (Aug. 1996) <b>2</b> (8):1327-1333	
	152	van TRIEST et al. "Thymidylate synthase level as the main predictive parameter for sensitivity to 5-fluorouracil, but not for folate-based thymidylate synthase inhibitors, in 13 nonselected colon cancer cell lines" <i>Clin. Cancer Res.</i> (Mar. 1999) <b>5</b> (3):643-654	
	153	WAHBA and FRIEDKIN "Direct spectrophotometric evidence for the oxidation of tetrahydrofolate during the enzymatic synthesis of thymidylate" <i>J. Biol. Chem.</i> (Mar. 1961) <b>236</b> (3):C11-C12	
	154	WALLIS et al. "Synthesis and anti-HIV activity of C4-modified pyrimidine nucleosides" <i>Il Farmaco</i> (1999) <b>54</b> :83-89	
	155	WANG "Protease Inhibitors as potential anti-viral agents for the treatment of picornaviral infections" <i>Prog. Drug Res.</i> (1999) <b>52</b> :197-219	
	156	WATAYA et al. "trans-5-(3,3,3-trifluoro-1-propenyl)-2'-deoxyuridylate: A mechanism-based inhibitor of thymidylate synthetase" <i>J. Med. Chem.</i> (Apr. 1979) <b>22</b> (4):339-340	
	157	WATAYA et al. "Interaction of thymidylate synthetase with 5-nitro-2'-deoxyuridylate" <i>J. Biol. Chem.</i> (June 25, 1980) <b>255</b> (12):5538-5544	
	158	WETTERGREN et al. "Drug-specific rearrangements of chromosome 12 in hydroxyurea-resistant mouse SEWA cells: Support for chromosomal breakage model of gene amplification" <i>Somat. Cell Molec. Gen.</i> (1994) <b>20</b> (4):267-285	

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	159	WHALEN and BOYER "Human glutathione S-transferases" <i>Seminars in Liver Disease</i> (1998) <b>18(4):345-358</b>	
	160	WILDNER et al. "Enzyme prodrug gene therapy: Synergistic use of the herpes simplex virus-cellular thymidine kinase/ganciclovir system and thymidylate synthase inhibitors for the treatment of colon cancer" <i>Cancer Res.</i> (Oct. 15, 1999) <b>59(20):5233-5238</b>	
	161	WOLFE et al. "Antibody-directed enzyme prodrug therapy with the T268G mutant of human carboxypeptidase A1: in vitro and in vivo studies with prodrugs of methotrexate and the thymidylate synthase inhibitors GW1031 and GW1843" <i>Bioconjugate Chem.</i> (1999) <b>10(1):38-48</b>	
	162	YEN et al. "Characterization of a hydroxyurea-resistant human KB cell line with supersensitivity to 6-thioguanine" <i>Cancer Res.</i> (July 15, 1994) <b>54:3686-3691</b>	
	163	ZEID et al. "Synthesis of new thiolated acyclonucleosides with potential anti-HBV activity" <i>Nucleos. Nucleot.</i> (1999) <b>18(1):95-111</b>	
	164	ANDERSEN et al. "Detection of C-ERBB-2 related protein in sera from breast cancer patients" <i>Acta Oncol.</i> (1995) <b>34(4):499-504</b>	
	165	AYISI et al. "Comparison of the antiviral effects of 5-methoxymethyldeoxyuridine-5'-monophosphate with adenine arabinoside-5'-monophosphate" <i>Antivir. Res.</i> (1983) <b>3:161-174</b>	
	166	BALZARINI et al. "Thymidylate synthase is the principal target enzyme for the cytostatic activity of (E)-5-(2-bromovinyl)-2'-deoxyuridine against murine mammary carcinoma (FM3A) cells transformed with the herpes simplex virus type 1 or type 2 thymidine kinase gene" <i>Mol. Pharmacol.</i> (1987) <b>32:410-416</b>	
	167	BALZARINI et al. "Differential mechanism of cytostatic effect of (E)-5-(2-bromovinyl)-2'-deoxyuridine, 9-(1,3-dihydroxy-2-propoxymethyl)guanine, and other antiherpetic drugs on tumor cells transfected by the thymidine kinase gene of herpes simplex virus type 1 or type 2" <i>J. Biol. Chem.</i> (1993) <b>268(9):6332-6337</b>	
	168	BALZARINI et al. "Anti-HIV and anti-HBV activity and resistance profile of 2',3'-dideoxy-3'-thiacytidine (3TC) and its arylphosphoramidate derivative CF 1109" <i>Biochem. Biophys. Res. Co.</i> (1996) <b>225:363-369</b>	
	169	BALZARINI et al. "Conversion of 2',3'-dideoxyadenosine (ddA) and 2',3'-dideoxy-2',3'-dideoxyadenosine (d4A) to their corresponding aryloxyphosphoramidate derivatives markedly potentiates their activity against human immunodeficiency virus and hepatitis B virus" <i>FEBS Lett.</i> (1997) <b>410:324-328</b>	
	170	BARR "Inhibition of thymidylate synthetase by 5-alkynyl-2'-deoxyuridylates" <i>J. Med. Chem.</i> (1981) <b>24(12):1385-1388</b>	

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	172	BERGSTROM et al. "C-5-substituted pyrimidine nucleosides. 3. Reaction of allylic chlorides, alcohols, and acetates with pyrimidine nucleoside derived organopalladium intermediates" <i>J. Org. Chem.</i> (1981) <b>46(7)</b> :1432-1441	
	173	BERKOW et al. (eds), <i>The Merck Manual of Diagnosis and Therapy</i> , 16th Edition, Merck & Co., Rahway, NJ, (May 1992) only page 1278 supplied	
	174	BOSSLET et al. "A novel one-step tumor-selective prodrug activation system" <i>Tumor Targeting</i> (1995) <b>1</b> :45-50	
	175	BOSSLET et al. "Elucidation of the mechanism enabling tumor selective prodrug monotherapy" <i>Cancer Res.</i> (Mar 15, 1998) <b>58</b> :1195-1201	
	176	BRISON "Gene amplification and tumor progression" <i>Biochim. Biophys. Acta</i> (1993) <b>1155</b> :25-41	
	177	CARL et al. "Protease-activated 'prodrugs' for cancer chemotherapy" <i>PNAS USA</i> (April 1980) <b>77(4)</b> :2224-2228	
	178	CAVA and LEVINSON "Thionation reactions of Lawesson's reagents" <i>Tetrahedron</i> (1985) <b>41(22)</b> :5061-5087	
	179	CHAKRAVARTY et al. "Plasmin-activated prodrugs for cancer chemotherapy. 2. Synthesis and biological activity of peptidyl derivatives of doxorubicin" <i>J. Med. Chem.</i> (1983) <b>26(5)</b> :638-644	
	180	COLACINO "Mechanisms for the anti-hepatitis B virus activity and mitochondrial toxicity of fialuridine (FIAU)" <i>Antivir. Res.</i> (1996) <b>29</b> :125-139	
	181	COLLINS et al. "Suicide prodrugs activated by Thymidylate synthase: Rationale for treatment and noninvasive imaging of tumors with deoxyuridine analogues" <i>Clin. Cancer Res.</i> (August 1999) <b>5</b> :1976-1981	
	182	CONNORS "Prodrugs in cancer chemotherapy" <i>Xenobiotica</i> (1986) <b>16(10/11)</b> :975-988	
	183	CONNORS "Is there a future for cancer chemotherapy?" <i>Ann. Oncol.</i> (1996) <b>7</b> :445-452	
	184	DAGLE et al. "Targeted degradation of mRNA in Xenopus oocytes and embryos directed by modified oligonucleotides: Studies of An2 and Cyclin in embryogenesis" <i>Nucleic Acids Res.</i> (Aug. 25, 1990) <b>18(16)</b> :4751-4757	
	185	DAVISSON et al. "Expression of human thymidylate synthase in <i>Escherichia coli</i> " <i>J. Biol. Chem.</i> (1989) <b>264(16)</b> :9145-9148	

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	186	DAVISSON et al. "Expression of human thymidylate synthase in <i>Escherichia coli</i> . (Additions and corrections)" <i>J. Biol. Chem.</i> (Dec. 2, 1994) <b>269(48)</b> :30740	
	187	DeCLERCQ "In search of a selective antiviral chemotherapy" <i>Clin. Microbiol. Rev.</i> (Oct. 1997) <b>10(4)</b> :674-693	
	188	DRAKE et al. "Resistance to Tomudex (ZD1694): Multifactorial in Human Breast and Colon Carcinoma Cell Lines" <i>Biochem. Pharmacol.</i> (1996) <b>51(10)</b> :1349-1355	
	189	ECCLES et al. "Significance of the c-erbB family of receptor tyrosine kinases in metastatic cancer and their potential as targets for immunotherapy" <i>Invasion Metastasis</i> (1994-95) <b>14(1-6)</b> :337-348	
	190	EISENBRAND et al. "An approach towards more selective anticancer agents" <i>J. Synthetic Organic Chem.</i> (1996) <b>10</b> :1246-1258	
	191	EVARD et al. "An <i>in vitro</i> nucleoside analog screening method for cancer gene therapy" <i>Cell Biol. Toxicol.</i> (1996) <b>12</b> :345-350	
	192	EVARD et al. "An <i>in vitro</i> nucleoside analog screening method for cancer gene therapy" <i>Chem. Abstracts</i> (1996) <b>126</b> :Abstract No. 26514	
	193	FELIP et al. "Overexpression of c-erbB-2 in epithelial ovarian cancer" <i>Cancer</i> (Apr. 15, 1995) <b>75(8)</b> :2147-2152	
	194	FINCH "Radiation Injury" <i>In: Harrison's Principles of Internal Medicine</i> , 12th Edition, McGraw-Hill, Inc., New York, NY (1991) 2204-2208	
	195	FINER-MOORE et al. "Refined structures of substrate-bound and phosphate-bound thymidylate synthase from <i>Lactobacillus casei</i> " <i>J. Mol. Biol.</i> (1993) <b>232</b> :1101-1116	
	196	FINER-MOORE et al. "Crystal structure of thymidylate synthase from T4 phage: Component of a deoxynucleoside triphosphate-synthesizing complex" <i>Biochemistry</i> (1994) <b>33</b> :15459-15468	
	197	FIRESTONE et al. "A comparison of the effects of antitumor agents upon normal human epidermal keratinocytes and human squamous cell carcinoma" <i>J. Invest. Dermatol.</i> (May 1990) <b>94(5)</b> :657-661	
	198	FIRESTONE et al. "A comparison of the effects of antitumor agents upon normal human epidermal keratinocytes and human squamous cell carcinoma" <i>Chem Abstracts</i> (1990) <b>113</b> :Abstract No. 254	
	199	GARRETT et al. "Thymidylate synthetase. Catalysis of dehalogenation of 5-bromo- and 5-iodo-2'-deoxyuridylate" <i>Biochemistry</i> (1979) <b>18(13)</b> :2798-2804	
	200	GOLDBERG et al. "Novel cell imaging techniques show induction of apoptosis and proliferation in mesothelial cells by asbestos" <i>Am. J. Respir. Cell Mol. Biol.</i> (1997) <b>17</b> :265-271	

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	201	GROS et al. "Isolation and expression of a complementary DNA that confers multidrug resistance" <i>Nature</i> (Oct. 1986) <b>323</b> :728-731	
	202	GROS et al. "Mammalian multidrug resistance gene: Complete cDNA sequence indicates strong homology to bacterial transport proteins" <i>Cell</i> (Nov. 7, 1986) <b>47</b> :371-380	
	203	GROS et al. "Isolation and characterization of DNA sequences amplified in multidrug-resistant hamster cells" <i>PNAS USA</i> (Jan. 1986) <b>83</b> :337-341	
	204	GUDKOV et al. "Cloning and characterization of DNA sequences amplified in multidrug-resistant djungarian hamster and mouse cells" <i>Somat. Cell Mol. Genet.</i> (1987) <b>13</b> (6):609-619	
	205	HAKIMELAHI et al. "Design, synthesis and structure-activity relationship of novel dinucleotide analogs as agents against herpes and human immunodeficiency viruses" <i>J. Med. Chem.</i> (Nov. 10, 1995) <b>38</b> (23):4648-4659	
	206	HARDY et al. "Atomic structure of thymidylate synthase: Target for rational drug design" <i>Science</i> (Jan. 23, 1987) <b>235</b> :448-455	
	207	HARRIS et al. "Adenovirus-mediated p53 gene transfer inhibits growth of human tumor cells expressing mutant p53 protein" <i>Cancer Gene Ther.</i> (1996) <b>3</b> (2):121-130	
	208	HASHIMOTO et al. "Simple separation of tritiated water and [ <sup>3</sup> H]deoxyuridine from [5- <sup>3</sup> H]deoxyuridine 5'-monophosphate in the thymidylate synthase assay" <i>Anal. Biochem.</i> (1987) <b>167</b> :340-346	
	209	HENGSTSCHLÄGER et al. "The role of p16 in the E2F-dependent thymidine kinase regulation" <i>Oncogene</i> (1996) <b>12</b> :1635-1643	
	210	HOLÝ et al. "Structure-Antiviral Activity Relationship in the Series of Pyrimidine and Purine N-[2-(2-Phosphonomethoxy)ethyl] Nucleotide Analogues. 1. Derivatives Substituted at the Carbon Atoms of the Base" <i>J. Med. Chem.</i> (1999) <b>42</b> (12):2064-2086	
	211	HORIKOSHI et al. "Quantitation of thymidylate synthase, dihydrofolate reductase, and DT-diaphorase gene expression in human tumors using the polymerase chain reaction" <i>Cancer Res.</i> (Jan. 1, 1992) <b>52</b> :108-116	
	212	HORN et al. "Fialuridine is phosphorylated and inhibits DNA synthesis in isolated rat hepatic mitochondria" <i>Antivir. Res.</i> (1997) <b>34</b> :71-74	
	213	HUANG and SANTI "Active site general catalysts are not necessary for some proton transfer reactions of thymidylate synthase" <i>Biochemistry</i> (1997) <b>36</b> :1869-1873	
	214	HUDZIAK et al. "Selection for transformation and met protooncogene amplification in NIH 3T3 fibroblasts using tumor necrosis factor $\alpha$ " <i>Cell Growth &amp; Differentiation</i> (1990) <b>1</b> :129-134	

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Sheet 16 of 19

**Complete if Known**

Application Number	10/681,418
Filing Date	October 7, 2003
First Named Inventor	H. Michael SHEPARD
Art Unit	Lawrence E. Crane
Examiner Name	1623
Attorney Docket Number	NB 2008.01

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	215	HUSAK et al. "Pseudotumour of the tongue caused by herpes simplex virus type 2 in an HIV-1 infected immunosuppressed patient" <i>Brit. J. Dermatol.</i> (1998) <b>139</b> :118-121	
	216	IMAI et al. "Studies on phosphorylation. IV. Selective phosphorylation of the primary hydroxyl group in nucleosides" <i>J. Org. Chem.</i> (June 1969) <b>34(6)</b> :1547-1550	
	217	JOHNSTON et al. "Production and characterization of monoclonal antibodies that localize human thymidylate synthase in the cytoplasm of human cells and tissue" <i>Cancer Res.</i> (Dec. 15, 1991) <b>51</b> :6668-6676	
	218	JOHNSTON "The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer" <i>J. Clin. Oncol.</i> (Dec. 1994) <b>12(12)</b> :2640-2647	
	219	KAMB "Cyclin-dependent kinase inhibitors and human cancer" <i>Curr. Top. Microbiol. Immunol.</i> (1998) <b>227</b> :139-148	
	220	KATKI et al. "Prodrugs activated by thymidylate synthase: Treatment of tumors with deoxyuridine analogs" <i>Proc. Amer. Assoc. Cancer Res.</i> (March 1998) <b>39</b> :Abstract No. 1275	
	221	KLECKER et al. "Toxicity, metabolism, DNA incorporation with lack of repair, and lactate production for 1-(2'-fluoro-2'-deoxy- $\beta$ -D-arabinofuranosyl)-5-iodouracil in U-937 and MOLT-4 cells" <i>Mol. Pharmacol.</i> (1994) <b>46</b> :1204-1209	
	222	KNIGHTON et al. "Structure of and kinetic channelling in bifunctional dihydrofolate reductase-thymidylate synthase" <i>Nature Struct. Biol.</i> (March 1994) <b>1(3)</b> :186-194	
	223	KODAMA et al. "Evaluation of antiherpetic compounds using a gastric cancer cell line: Pronounced activity of BVDU against herpes simplex virus replication" <i>Microbiol. Immunol.</i> (1996) <b>40(5)</b> :359-363	
	224	KUMAR et al. "Synthesis and biological evaluation of some cyclic phosphoramidate nucleoside derivatives" <i>J. Med. Chem.</i> (Sept. 1990) <b>33(9)</b> :2368-2374	
	225	KUNDU et al. "Synthesis and biological activities of [E]-5-(2-acylviny) uracils" <i>Eur. J. Med. Chem.</i> (1993) <b>28</b> :473-479	
	226	KUROBOSHI and HIYAMA "A facile synthesis of difluoromethylene compounds by oxidative fluorodesulfurization of dithioacetals using tetrabutylammonium dihydrogentrifluoride and N-halo compounds" <i>SYNLETT</i> (Dec. 1991) pp. 909-910	
	227	KUROBOSHI and HIYAMA "A facile synthesis of $\alpha,\alpha$ -difluoroalkyl ethers and carbonyl fluoride acetals by oxidative desulfurization-fluorination" <i>SYNLETT</i> (April 1994) pp. 251-252	
	228	LAM "Application of combinatorial library methods in cancer research and drug discovery" <i>Anti-Cancer Drug Design</i> (1997) <b>12</b> :145-167	
	229	LARSSON et al. "Thymidylate synthase in advanced gastrointestinal and breast cancers" <i>Acta Oncologica</i> (1996) <b>35(4)</b> :469-472	

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	230	LI et al. "Lack of functional retinoblastoma protein mediates increased resistance to antimetabolites in human sarcoma cell lines" <i>PNAS USA</i> (Oct. 1995) <b>92</b> :10436-10440	
	231	LIVINGSTONE et al. "Altered cell cycle arrest and gene amplification potential accompany loss of wild-type p53" <i>Cell</i> (Sept. 18, 1992) <b>70</b> :923-935	
	232	MASTERS and ALTARDI "The nucleotide sequence of the cDNA coding for the human dihydrofolate acid reductase" <i>Gene</i> (1983) <b>21</b> :59-63	
	233	McGUIGAN "Aryl phosphate derivatives of AZT retain activity against HIV1 in cell lines which are resistant to the action of AZT" <i>Antivir. Res.</i> (1992) <b>17</b> :311-321	
	234	McGUIGAN "Intracellular delivery of bioactive AZT nucleotides by aryl phosphate derivatives of AZT" <i>J. Med. Chem.</i> (1993) <b>36</b> :1048-1052	
	235	McGUIGAN "Aryl phosphoramidate derivatives of d4T have improved anti-HIV efficacy in tissue culture and may act by the generation of a novel intracellular metabolite" <i>J. Med. Chem.</i> (1996) <b>39</b> :1748-1753	
	236	McGUIGAN et al. "Synthesis and evaluation of some masked phosphate esters of the anti-herpetic drug 882C (netivudine) as potential antiviral agents" <i>Antivir. Chem. Chemoth.</i> (1998) <b>9</b> :187-197	
	237	McKAY et al. "Broad spectrum aminoglycoside phosphotransferase type III from <i>Enterococcus</i> : Overexpression, purification, and substrate specificity" <i>Biochemistry</i> (1994) <b>33</b> :6936-6944	
	238	MEDEN et al. "Elevated serum levels of a c-erbB-2 oncogene product in ovarian cancer patients and in pregnancy" <i>J. Cancer Res. Clin. Oncol.</i> (1994) <b>120</b> :378-381	
	239	MONTFORT and WEICHSEL "Thymidylate synthase: Structure, inhibition, and strained conformations during catalysis" <i>Pharmacol. Ther.</i> (1997) <b>76</b> (1-3):29-43	
	240	MONTGOMERY et al., "Phosphonate analogue of 2'-deoxy-5-fluorouridylic acid" <i>J. Med. Chem.</i> (1979) <b>22</b> (1):109-111	
	241	MORRISON & BOYD (eds) <i>Organic Chemistry</i> , Allyn & Bacon, Inc., Boston, MA, (1973) only pages 1170-1180 supplied	
	242	MURAKAMI and SEKIYA "Accumulation of genetic alterations and their significance in each primary human cancer and cell line" <i>Mutat. Res.</i> (1998) <b>400</b> (1-2):421-437	
	243	NAESENS et al. "Anti-HIV activity and metabolism of phosphoramidate derivatives of D4T-MP with Variations in the amino acid moiety" Poster Session 1, <u>The Tenth International Conference on Antiviral Research</u> , Hotel Nikko, Atlanta, GA April 6-11, 1997; published in <i>Antivir. Research</i> (April 1997) <b>34</b> (2):A54 (Abstract 40)	
	244	NAKANO et al., "Critical role of phenylalanine 34 of human dihydrofolate reductase in substrate and inhibitor binding and in catalysis" <i>Biochemistry</i> (1994) <b>33</b> :9945-9952	

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	245	NOOTER and STOTER "Molecular mechanisms of multidrug resistance in cancer chemotherapy" <i>Path. Res. Pract.</i> (1996) <b>192</b> :768-780	
	246	OSAKI et al. "5-fluorouracil (5-FU) induced apoptosis in gastric cancer cell lines: Role of the p53 gene" <i>Apoptosis</i> (1997) <b>2</b> :221-226	
	247	OSHIRO et al. "Genotoxic properties of (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)" <i>Fundam. Appl. Toxicol.</i> (1992) <b>18</b> :491-498	
	248	PARDO et al. "The incorporation of deoxyuridine monophosphate in DNA increases the sister-chromatid exchange yield" <i>Exp Cell Res.</i> (1987) <b>168</b> :507-517	
	249	PARK et al. "Chemotherapy efficacy of E-5-(2-bromovinyl)-2'-deoxyuridine for orofacial infection with herpes simplex virus type 1 in mice" <i>J. Infectious Diseases</i> (June 1982) <b>145</b> (6):909-913	
	250	PERRY et al. "Plastic adaptation toward mutations in proteins: Structural comparison of thymidylate synthases" <i>Proteins</i> (1990) <b>8</b> :315-333	
	251	PETERS et al. "Thymidylate synthase and drug resistance" <i>Eur. J. Can.</i> (1995) <b>31A</b> (7/8):1299-1305	
	252	PUPA et al. "The extracellular domain of the c-erbB-2 oncoprotein is released from tumor cells by proteolytic cleavage" <i>Oncogene</i> (1993) <b>8</b> :2917-2923	
	253	ROBERTS "An isotopic assay for thymidylate synthetase" <i>Biochemistry</i> (Nov. 1966) <b>5</b> (11):3546-3548	
	254	ROGULSKI et al. "Glioma cells transduced with an <i>Escherichia coli</i> CD/HSV-1 TK fusion gene exhibit enhanced metabolic suicide and radiosensitivity" <i>Hum. Gene Ther.</i> (Jan. 1, 1997) <b>8</b> :73-85	
	255	RONINSON et al. "Amplification of specific DNA sequences correlates with multi-drug resistance in Chinese hamster cells" <i>Nature</i> (June 14, 1984) <b>309</b> :626-628	
	256	SAUTER et al. "Heterogeneity of erbB-2 gene amplification in bladder cancer" <i>Cancer Res.</i> (May 15, 1993) <b>53</b> :2199-2203	
	257	SCHIFFER et al. "Crystal structure of human thymidylate synthase: A structural mechanism for guiding substrates into the active site" <i>Biochemistry</i> (1995) <b>34</b> :16279-16287	
	258	SCHIMKE "Gene amplification in cultured cells" <i>J. Biol. Chem.</i> (May 5, 1988) <b>263</b> (13):5989-5992	
	259	SEGOVIA "Leishmania gene amplification: A mechanism of drug resistance" <i>Ann. Trop. Med. Parasit.</i> (1994) <b>88</b> (2):123-130	
	260	SINGH et al. "Studies on the preparation and isomeric composition of <sup>186</sup> Re- and <sup>188</sup> Re-pentavalent rhenium dimercaptosuccinic acid complex" <i>Nucl. Med. Commun.</i> (1993) <b>14</b> :197-203	
	261	SLAMON et al. "Human breast cancer: Correlation of relapse and survival with amplification of the HER-2/ <i>neu</i> oncogene" <i>Science</i> (Jan. 9, 1987) <b>235</b> :177-182	
	262	SLAMON et al. "Studies of the HER-2/ <i>neu</i> proto-oncogene in human breast and ovarian cancer" <i>Science</i> (May 12, 1989) <b>244</b> :707-712	

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	263	SNYDMAN et al. "Analysis of trends in antimicrobial resistance patterns among clinical isolates of <i>Bacteroides fragilis</i> group species from 1990 to 1994" <i>Clin. Infect. Dis.</i> (1996) <b>23</b> (Suppl. 1):S54-S65	
	264	STASCHKE et al. "The in vitro anti-hepatitis B virus activity of FIAU [1-(2'-deoxy-2'-fluro-1- $\beta$ -D-arabinofuranosyl-5-iodo)uracil] is selective, reversible, and determined, at least in part, by the host cell" <i>Antiviral Res.</i> (1994) <b>23</b> :45-61	
	265	STOUT et al. "Structure-based design of inhibitors specific for bacterial thymidylate synthase" <i>Biochemistry</i> (1999) <b>38</b> :1607-1617	
	266	SUKUMAR and BARBACID "Specific patterns of oncogene activation in transplacentally induced tumors" <i>PNAS USA</i> (Jan. 1990) <b>87</b> :718-722	
	267	TAKEISHI et al. "Nucleotide sequence of a functional cDNA for human thymidylate synthase" <i>Nucl. Acid Res.</i> (1985) <b>13</b> (6):2035-2043	
	268	TENNANT et al. "Antiviral activity and toxicity of fialuridine in the woodchuck model of hepatitis B virus infection" <i>Hepatology</i> (July 1998) <b>28</b> (1):179-191	
	269	TOWNSEND (eds), <i>Chemistry of Nucleosides and Nucleotides</i> , Vol. 3, Plenum Press, New York, NY (1974) only Table of Contents, Bibliography, pages 529-535 and Index pp. 537-552 supplied	
	270	UBEDA and HABENER "The large subunit of the DNA replication complex C (DSEB/RF-C140) cleaved and inactivated by Caspace-3 (CPP32/YAMA) during fas-induced apoptosis" <i>J. Biol. Chem.</i> (Aug. 1, 1997) <b>272</b> (31):19562-19568	
	271	van de VIJVER et al. "Amplification of the <i>neu</i> (c- <i>erbB</i> -2) oncogene in human mammary tumors is relatively frequent and is often accompanied by amplification of the linked c- <i>erbA</i> oncogene" <i>Mol. Cell. Biol.</i> (May 1987) <b>7</b> (5):2019-2023	
	272	VOLM et al. "Relationship of inherent resistance to doxorubicin, proliferative activity and expression of P-glycoprotein 170, and glutathione S-transferase- $\pi$ in human lung tumors" <i>Cancer</i> (Aug. 15, 1992) <b>70</b> (4):764-769	
	273	WANG et al. "Identification and characterization of Ich-3, a member of the interleukin-1 $\beta$ converting enzyme (ICE)/Ced-3 family and an upstream regulator of ICE" <i>J. Biol. Chem.</i> (Aug. 23, 1996) <b>271</b> (34):20580-20587	
	274	YIN et al. "Wild-type p53 restores cell cycle control and inhibits gene amplification in cells with mutant p53 alleles" <i>Cell</i> (Sept. 18, 1992) <b>70</b> :937-948	
	275	ZHOU et al. "Target protease specificity of the viral serpin CrmA" <i>J. Biol. Chem.</i> (Mar. 21, 1997) <b>272</b> (12):7797-7800	
	276	<u>The American Heritage College Dictionary</u> , Third Edition, Houghton Mifflin Co., New York, NY (1997) only page 668 supplied	

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application for:

H. Michael SHEPARD et al.

Serial No.: 10/681,418

Filing Date: October 7, 2003

For: ENZYME CATALYZED THERAPEUTIC  
COMPOUNDS

Examiner: Lawrence E. Crane

Group Art Unit: 1623

INFORMATION DISCLOSURE STATEMENT

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Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR §§ 1.97 and 1.98, the items identified in this Information Disclosure Statement ("IDS") are brought to the attention of the Examiner for consideration in connection with the examination of the above-identified application. The items are listed on the attached forms PTO/SB/08a and PTO/SB/08b.

Copies of the following documents listed in PTO/SB/08a (Item Nos. 1-15, 17-60, 62-65, and 71-88) and copies of the following documents listed in PTO/SB/08b (Item Nos. 1-163) were previously cited by the Office or submitted in Information Disclosure Statements in related applications: U.S. Serial Numbers 09/235,961, filed January 22, 1999, now U.S. Patent No. 6,339,151; U.S. Serial No. 09/856,127, filed July 21, 2000 (U.S. Patent No. 6,683,061 issued January 27, 2004); U.S. Serial No. 09/782,721, filed February 12, 2001; U.S. Serial No. 09/990,799, filed November 16, 2001; and U.S. Serial No. 10/051,320, filed January 18, 2002, and accordingly, copies are not included herewith. The Examiner is requested to make these documents of record.

Pursuant to 37 CFR § 1.98(a)(2)(i), copies of the following items identified on form PTO/SB/08a under the heading U.S. Patent Documents (Item Nos. 66-70) are not attached.

Copies of the following documents listed in PTO/SB/08a (Item Nos. 16 and 61) and PTO/SB/08b (Item Nos. 164-275) are attached for consideration.

The Examiner is requested to make these documents of record.

This Information Disclosure Statement is submitted:



With the new patent application submitted herewith (37 C.F.R. § 1.97(a)).

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- ☐ Within three months of the application filing date or before receipt of a first Office Action on the merits; accordingly, no fee or separate requirements are required.
- ☐ Before the mailing date of the first Office Action on the merits. In the event, however that an Office Action has crossed in the mail with this Information Disclosure Statement, the Commissioner is hereby authorized to charge Deposit Account No. 50-1189 for any fees required pursuant to 37 C.F.R. §§ 1.17(p) or 1.17(i)(1).
- ☒ After receipt of a first Office Action on the merits but before a final Office Action or Notice of Allowance. A fee is required. The Commissioner is hereby authorized to charge Deposit Account No. 50-1189 for any fees required pursuant to 37 C.F.R. §§ 1.17(p) or 1.17(i)(1).
- ☐ After receipt of a final Office Action or Notice of Allowance, but before payment of the issue fee. Accordingly, a Certification under 37 C.F.R. § 1.97(e) is provided herein. The Commissioner is hereby authorized to charge Deposit Account No. 50-1189 for any fees required pursuant to 37 C.F.R. §§ 1.17(p) or 1.17(i)(1).

The undersigned certifies that:

- ☐ Each item of information contained in the Information Disclosure Statement was first cited in any communication mailed from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.
- ☐ No item of information contained in this information disclosure statement was cited in a communication mailed from a foreign patent office in a counterpart foreign application or, to the knowledge of the undersigned after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Information Disclosure Statement.

Applicants would appreciate the Examiner initialing and returning the Form PTO-1449, indicating that the information has been considered and made of record herein.

This Information Disclosure Statement under 37 C.F.R. § 1.97 is not to be construed as a representation that: (i) a complete search has been made; (ii) additional information material to the examination of this application does not exist; (iii) the information, protocols, results and the like reported by third parties are accurate or enabling; or (iv) the above information constitutes prior art to the subject invention.

In the unlikely event that the transmittal letter is separated from this document and the U.S. Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 50-1178 referencing 7008303001. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: \_\_\_\_\_

*Aug. 6, 2004*

By: \_\_\_\_\_

*Antoinette F. Konski*

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